The Behaviour of Ethyl 1-acetyl-4-aryl-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-ylimidoformate Towards Nucleophiles

M. E. A. Zaki, E. M. Morsy, F. M. Abdel-Motti and F. M. E. Abdel-Megeid
Photochemistry department, National Research Centre
Dokki,Cairo,Egypt
e-mail: meazaki@nrc.org.eg

Abstract: Ethyl 1-acetyl-4-aryl-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-ylimidoformate **4**a,b undergoes nucleophilic attack by ammonia solution, hydrazine hydrate and appropriate carboxylic acid hydrazides affording **5**,**7**a,b,,**8**a,b respectively. Cyclocondensation of **7**a,b with carbon donor reagents took place affording **9**a-d, **10**,**12**a-c, **13**a,b. Reaction of **7**a,b towards aldehydes was investigated in presence of acid and base.

Introduction

The chemistry of pyrazole derivatives especially 1,4-dihydro-5H-pyrazol-5-one and 3-methyl-1-phenyl-1,4-dihydro-5H-pyrazol-5-one has received great interest since they are the parent skeleton of pyrine drugs such as antipyrine and amino-pyrine and other medicinal compounds.[1-3] Moreover, the biological activities of pyrano[2,3-c]pyrazole derivatives as analgesic and anti-inflammatory agents,[4] cardiotonic agents,[5] molluscicides,[6] bactericides,[7] and virucides[8] have led to extensive research for their synthesis

Results and Discussion:

In the past few years, we have involved in a program[9] aimed at developing new efficient synthesis of these heteroaromatic compounds utilizing inexpensive starting materials . During this phase of our research, we reported here that 6-amino-1,4-dihydro-3-methyl-4-(3-methoxy-phenyl)pyrano[2,3-c]pyrazole-5-carbonitrile **3**a and 6-amino-1,4-dihydro-3-methyl-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile **3**b as key compounds for this study and for further syntheses. Thus, 3-methyl-2-pyrazolin-5-one **1** reacts with *m*-methoxy-benzylidenemalononitrile **2a** and *p*-nitrobenzylidenemalono-nitrile **2**b to give the corresponding pyrazolopyran derivatives **3**a,b , respectively.

Treatment of compounds **3**a,b with an equimolar amount of triethyl orthoformate in the presence of acetic anhydride gave a major product which could be assigned the structure of ethyl 1- or 2-acetyl-**4**-aryl-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-ylimidoformate **4**a,b or **5**a,b, respectively (due to possible tautomerism).Scheme 1.

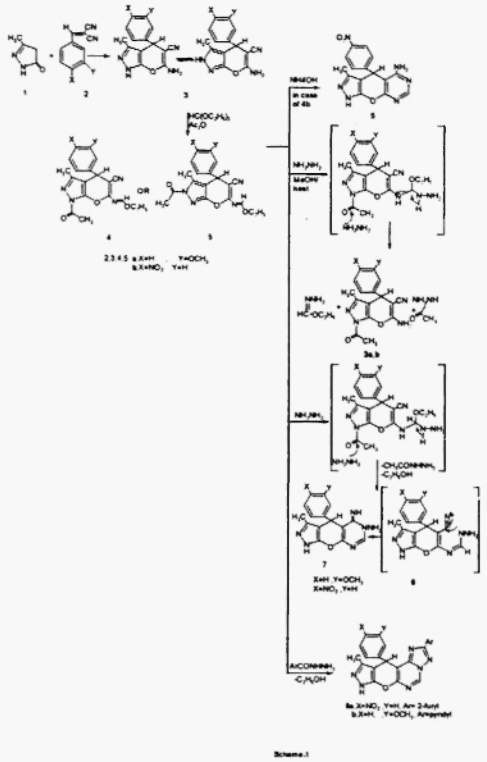
Actually, inspection of the ^{1}H NMR spectra of the two products **4**a,b or **5**a,b revealed that the C^3-methyl protons signal appeared at δ 2.17 and δ 2.1 ppm, respectively. This is in favor of assignment of structures **4**a,b for the reaction products since the C^3-methyl protons of structures **5**a,b are adjacent to the N^2-acetyl group and so they are more deshielded and their signal would have been observed at lower field. This assignment is in accordance with the ^{1}H NMR spectral data given by many authors[10-11] for alkylation and acylation reactions. Moreover, ^{13}C NMR spectrum of compound **4**a gives further confirmation for its assigned structure since it showed the following charactristic signals at (δ, ppm) corresponding to: 157.44 (C^3), 155.58 (C^{7a}),13.8 (C^{10}), These spectral data are in agreement with the observed data for C^3, C^{10}, and C^{7a} of related N^1-alkyl compounds.[12]

The reactivity of **4**a,b towards N-nucleophiles namely ammonia solution , hydrazine hydrate and carboxylic acid hydrazide derivatives took place under this investigation. When a mixture of compound **4**b and concentrated solution of ammonium hydroxide afforded **5**, as an unexpected product, where deacetylation of the N^1-acetyl group took place.

The interaction of the imidatoformate **4**b with hydrazine hydrate in methanol at reflux temperature caused the deacetylation of N^1-acetyl group besides the elimination of the ethoxymethine group as ethyl formate hydrazone to give again the β-enaminonitrile **3**b. Scheme 1.

However, treatment of compound **4**a,b with hydrazine hydrate for 1 h at 0°C caused deacetylation of the N^1-acetyl group and cycloaddition to yield 4-aryl-1,**4**-dihydroiminopyrazolo[4`,3`:5,6]pyrano[2,3-d]pyrimidin-6-amine **7**a,b, respectively, presumably *via* intermediacy of **6**a,b which could be formed by nucleophilic substitution.

An improvement in the formation of the triazolo [1,5-c] pyrimidine derivatives in an one-pot reaction by using carboxylic acid hydrazide derivatives **4**a,b afforded **8**a and **8**b respectively, where also deacetylation of the N^1-acetyl group was observed. Scheme 1



Since some pronounced biological activities were evaluated for [1,2,4]triazolopyrimidine derivatives, e.g. analgesic,[13] antibacterial,[14] and C.N.S derpressing[15] activities, it thought it would be useful to prepare some derivatives of pyranopyrazoles incorporating the thiazolopyrimidine moiety to enhance their biological activity.

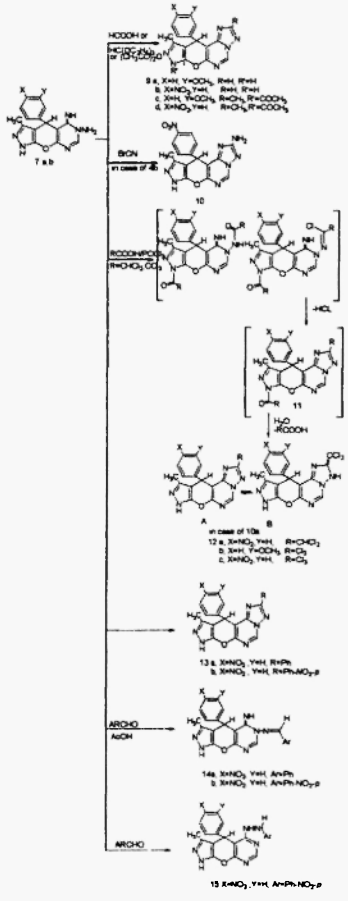
Therefore, When 7a,b reacted with one-carbon donar cyclizing agents they afforded the corresponding [1,2,4]triazolo[1,5-c]pyrimidine derivatives. Thus, cyclocondensation of 7a,b with formic acid or triethyl orthoformate and acetic anhydride gave **9**a-d respectively.
When a mixture of 7b and cyanogen bromide in dimethyl formamide was heated for 5 h, 8,11-dihydro-10-methyl-11-(4-nitrophenyl) pyrazolo [4`,3`:5,6] pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-2-amine **10** was isolated.

A new simple and conveninet route to the formation of triazolo[1,5-c]pyrimidine took place *via* the reaction of appropriate halo carboxylic acid namely dichloroacetic acid and trichloroacetic acid with 7a,b in the presence of phosphoryl chloride afforded 2-dichloromethyl-, and 2-trichloromethyl- triazolo[1,5-c]-pyrimidine derivatives **12**a-c were formed, respectively. The ^{1}H NMR spectrum of compound **12**a is in favor of structure **B** which was established from its the ^{1}H NMR spectraum of compound **12**b showed characteristic signals at 7.4 (s, 1H, NH exchangeable with D_2O), 9.5 (s, H- pyrimidine), and 12.3 (s, NH-pyrazole).

We do believe that the generated acid chloride *in situ* caused the acylation for exo NH_2 and endo NH of pyrazole with formation of **11** as intermediate. Decompsition of excess phosphoryl chloride in crushed ice caused nucleophilic attack of water to the weak N-acetyl group.
When compound 7b was treated with benzoic acid or 4-nitrobenzoic acid in the presence of phosphorus oxychloride it yielded **13**a,b, respectively.

The difficulty of preparing substituted pyrazoles explains the lack of reports on their utility, as a result of nucleophilic attack to N-acyl or aroyl group.

In the present study and continuing our program , we report the reactivity of 7a,b,towards aldehyde in presence of base and acid medium. When compound 7b was treated with benzaldehyde or 4-nitrobenzaldehyde in the presence of acetic acid it gave 1,4-dihydro-5-imino-3-methyl-4-(4-nitrophenyl) pyrazolo[4`,3`:5,6]-pyrano[2,3-d]pyrimidin-6-benzylidene amine **14**a and -6-(4-nitrobenzylidene) amine **14**b,respectively. the ^{1}H NMR spectraum of compound **14**a showed signal at 8.3 (s, H-pyrimidine), 10.9 (br, NH-imino, exchangeable with D_2O).



However, when compound 7b was treated with 4-nitrobenzaldehyde in the presence of piperidine and heated at reflux temperature it afforded 1,4-dihydro-3-methyl-4-(4-nitro-phenyl)pyrazolo[4`,3`:5,6] pyrano [2,3-d] pyrimidin-5-yl-4-nitro-benzaldehyde hydrazone **15**, presumably *via* Dimroth rearrangement of 7b Scheme 2

EXPERIMENTAl

Melting points are uncorrected and were taken on Electrothermal A 9000 SERIES Digital melting Point Apparatus. Microanalyses were performed by the Central Services Laboratory NRC. (Satisfactory microanalysis were obtained C ± 0.40; H ± 0.27; N ± 0.30) . IR Spectra were recorded on Carlzeise spectrophotometer model "UR 10" using KBr. ^{1}H NMR and ^{13}C NMR spectra were determined on Varian Gemini 200 MHz using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Finnigan SSQ 7000 mass spectrometer.

6-Amino-4-aryl-1,4-dihydro-3-methylpyrano[2,3-c]-pyrazole-5-carbonitrile 3a,b

A solution of 3-methyl-2-pyrazolin-5-one **1**, 0.098g (0.001 mol), in ethanol (10 ml) was treated with m-methoxybenzylidene-malononitrile **2a**, 0.2g (0.001 mol) or p-nitrobenzylidene-malononitrile **2**b 0.2g (0.001 mol) in the presence of catalytic amount of piperidine. The reaction mixture was refluxed for 1h. The solid product so formed was collected by filteration and recrystallized from ethanol to give **3**a,b respectively.

6-Amino-4-(3-methoxyphenyl)-1,4-dihydro-3-methylpyrano[2,3-c]-pyrazole-5-carbonitrile 3a 80%, m.p. 230-232 °C, ^{1}H NMR of compound **3**a (*DMSO-d_6*, δ ppm): 1.6 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.5 (s, 1H, pyran), 6.6 (s, 2H, NH_2, exchangeable with D_2O), 6.7-7.2 (m, 4H, aromatic) and 12.1 (s, 1H, NH-pyrazole, exchangeable with D_2O), MS, m/z (%): 282 (M^+, 42%).

6-Amino-4-(4-nitrophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]-pyrazole-5-carbonitrile 3b 85%, m.p. 277-280°C, ^{1}H NMR (*DMSO-d_6*, δ ppm): 1.6 (s, 3H, CH_3), 4.7 (s, 1H, pyran), 7.0 (s, 2H, NH_2,

exchangeable with D_2O), 7.4 (d, 2H, 4-O_2NPh, ΔJ=*11Hz*), 8.2 (d, 2H, 4-O_2NPh, ΔJ=*11Hz*), 12.1 (s, 1H, NH pyrazole, exchangeable withD_2O). MS, m/z (%): 297 (M^+, 25%), 175 [(M-Ar)$^+$, 100%].

ethyl 1-acetyl-5-cyano-3-methyl-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-ylimidoformate 4a,b: A mixture of compounds **3**a 0.3g or **3**b 0.3g (0.001 mol), triethyl orthoformate 0.15g (0.001 mol) and acetic anhydride (3 ml) was refluxed for 5h. The reaction mixture was evaporated, the residue was collected by filtration, dried and recrystallized from petrolum ether (60-80) to give compound **4**a and **4**b respectively.

ethyl 1-acetyl-5-cyano-3-methyl-4-(3-methoxyphenyl)-1,4-dihydropyrano[2,3-*c*]pyrazol-6-ylimidoformate 4a, 80%, m.p. 170-172°C, (*DMSO-d_6*, δ ppm): 1.33 (t, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.6 (s, 3H, N-CO-CH_3), 3.75 (s, 3H, OCH_3), 4.3 (q, 2H, CH_2), 4.96 (s, 1H, H-pyran), 6.83-7.35 (m, 4H, aromatic) and 8.65 (s, 1H, N=CH).^{13}C NMR spectrum of compound **4**a (*DMSO-d_6*, δ ppm): 12.96 (C^{14}), 13.8 (C^{10}), 23.05 (C^9), 36.57 (O-CH_3 attached m- to the phenyl group), 55.07 (C^{13}), 64.19 (C^4), 81.62 (C^{12}), 105.03 (C^{3a}), 112.54, 114.25, 117.41, 130.02, 140.54, 142.89 (6 carbon atoms of the phenyl group), 120.16 (C^{11}), 155.58 (C^{7a}), 157.44 (C^3), 159.4 (C^5), 161.79 (C^6), 170.81 (C^8). MS, m/z (%): 380 (M^+, 27%), 273 [(M-Ar)$^+$, 43%] and 231 {[M-(Ar + Ac)]$^+$, 85%}.

ethyl 1-acetyl-5-cyano-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazol-6-ylimidoformate 4b, 85%, m.p. 160-163°C, (*DMSO-d_6*, δ ppm) ^{1}H NMR (*DMSO-d_6*, δ ppm): 1.4 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.7 (s, 3H, N-CO-CH_3), 4.3 (q, 2H, CH_2), 5.1 (s, 1H, H-pyran), 7.6 (d, 2H, 4-O_2N Ph, ΔJ=*11Hz*), 8.3 (d, 2H, 4-O_2N Ph, ΔJ=*11Hz*) and **8**.6 (s, 1H, N=CH). MS, m/z (%): 395 (M^+, 67%), 273 [(M-Ar)$^+$, 64%] and 231 {[M-(Ar + Ac)]$^+$, 100%}.

1,4-Dihydro-3-methyl-4-(4-nitrophenyl)pyrazolo[4`,3`: 5,6]pyrano[2,3-d]pyrimidin-5-amine 5: A mixture of compound **4**b 0.4g (0.001 mol), ammonium hydroxide (25%) (2 ml) in ethanol (5 ml) was stirred at 0°C for 3h. A solid was formed, then collected by filteration and recrystallized from ethanol to give 89% yield of compound **5**, m.p. 260-263°C. ^{1}H NMR *(DMSO-d_6*, δ ppm): 1.7 (s, 3H, CH_3), 5.0 (s, 1H, pyran), 7.5 (d, 2H, 4-O_2NPh, ΔJ=*11Hz*), 7.7 (s, 2H, NH_2 exchangeable with D_2O), **8**.3 (m, 3H, p.O_2NPh, ΔJ=*11Hz* + 1H-pyrimidine), and 12.2 (s, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 324 (M^+, 32%), 202 [(M-Ar)$^+$, 100%].

4-Aryl-1,4-dihydro-5-iminopyrazolo[4`,3`:5,6]pyrano-[2,3-d] pyrimidin-6-amine 7a,b: A mixture of compounds 4a 0.4g or 4b 0.4g (0.001 mol) in benzene (3 ml) was treated with hydrazine hydrate (98%) (0.5 ml) and stirring at 0°C for 1 h then stood overnight. A solid was formed, then collected by filteration and recrystallized from ethanol to give compounds 7a,b respectively.

1,4-dihydro-(3-methoxyphenyl)-5-iminopyrazolo[4`,3`:5,6]pyrano-[2,3-d] pyrimidin-6-amine 7a: 56%, m.p. 194-195°C, IR spectrum (KBr,ν, cm^{-1}): 3340 (NH_2), 3185 (NH), 1605 (C=N) and C=N is absent.^{1}H NMR (*DMSO-d_6*, δ ppm): 1.97 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 5.02 (s, 1H, pyran), 5.6 (s, 2H, NH_2 exchangeable with D_2O), 6.7-7.2 (m, 5H, aromatic + NH), 8.2 (s, 1H, pyrimidine) and 12.1 (s, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 324 (M^+, 34%), 308 [(M-NH_2)$^+$, 94%] and 202 {[M-(NH_2+Ar)]$^+$, 100%].

1,4-dihydro-(4-nitrophenyl)-5-iminopyrazolo[4`,3`:5,6]pyrano-[2,3-d] pyrimidin-6-amine 7b: 47%, m.p. 216-218°C, : IR spectrum (KBr,ν, cm^{-1}) : 3350 (NH_2), 3120 (NH), 1650 (C=N) and C=N is absent. ^{1}H NMR (*DMSO-d_6*, δ ppm): 1.9 (s, 3H, CH_3), 5.3 (s, 1H, pyran), 5.7 (s,2H,NH_2, exchangeable with D_2O), 7.3 (s, 1H, pyrimidine), 7.6 (d, 2H, 4-O_2NPh + NH), 8.2 (d, 2H, 4-O_2NPh, ΔJ=*11Hz*) and 12.1 (s, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 339 (M^+, 28%), 323 [(M-NH_2)$^+$, 100%] and 202 {[M-(NH_2+Ar)]$^+$, 26%}.

8,11-Dihydro-11-(3-methoxyphenyl)-10-methyl-2-(4-pyridyl)pyrazolo-[4`,3`:5,6]pyrano [2,3-e][1,2,4]triazolo-[1,5-c]pyeimidine 8a: A mixture of compound **4a,** 0.4g (0.001 mol) and pyridine-4-carbohydrazide 0.15g, (0.0012 mol) in ethanol (10 ml) was heated under reflux for 7 h then left to cool. The obtained solid was collected by filteration and recrystallized from ethanol afforded **8**a. 70% ,M.p. 290-292°C. ^{1}H NMR (*DMSO-d_6*, δ ppm): 2.0 (s, 3H, CH_3), 3.7 (s, 3H, OCH3), 5.5 (s, 1H, pyran), 6.7-7.3 (m, 4H, aromatic), 7.9 (d, 2H, pyridyl), 8.6 (d, 2H, pyridyl) and 8.7 (s, 1H, pyrimidine) and 12.3 (br, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 411 (M^+, 31%), 304 [(M-Ar)$^+$, 100%].

8,11-Dihydro-2-furyl-10-methyl-4-(4-nitrophenyl)-pyrazolo[4`,3`:5,6]pyrano[2,3-e][1,2,4]triazolo[1,5-c]-pyeimidine 8b: To a mixture of compound 4b, 0.4g (0.0011 mol) and furan-2-carbohydrazide, 0.13g (0.001 mole) in ethanole (10 ml). The reaction mixture was heated under reflux for 7 h. The obtained solid was collected by filteration and recrystallized from ethanol afforded 65%. M.p. 267-270°C. ^{1}HNMR (*DMSO-d_6*, δ ppm): 2.2 (s, 3H, CH_3), 5.6 (s, 1H, pyran), 6.5-7.0 (d, 3H, furan), 7.6-8.2 (d, 4H, aromatic), 8.7 (s, 1H, pyrimidine) and 12.5 (br, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 415 (M^+, 43%), 293 [(M-Ar)$^+$, 100%].

11-Aryl-8,11-dihydro-10-methylpyrazolo[4`,3`:5,6]-pyrano[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine 9a-d Equimolar amounts of compounds 7a 0.3g or 7b 0.3g (0.001 mol), triethyl orthoformate (10 ml),

and formic acid (10 ml),or acetic anhydride respectively, were heated under reflux for 8 h. The reaction mixture was evaporated. The residue was collected by filteration and recrystallized from methanol to give compounds **9**a-d, respectively

.8,11-dihydro-11(3-methoxyphenyl)-10-methlpyrazolo[4`,3`:5,6]-pyrano[2,3-e[[1,2,4]triazolo[1,5-c]pyrimidine 9a, 60%in case of formic acid and 80% in case of triethyl orthoformate,m.p 237-239^0 C,^{1}H NMR of compound **9**a *(CDCl$_3$,* δ ppm): 2.1 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 5.6 (s, 1H, pyran), 6.5-7.3 (m, 4H, aromatic), 8.3 (s, 1H, triazole), 9.2 (s, 1H, pyrimidine), and 12.3 (brs, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 334 (M^+, 38%), 227 [$(M\text{-}Ar)^+$, 100%]

8,11-dihydro-11-(4-nitrophenyl)-10-methylpyrazolo[4`,3`:5,6]-pyrano[2,3-e][1,2,4] triazolo[1,5-c]pyrimidine 9b: 65% in case of formic acid and 82% in case of triethyl orthoformate,m.p 240-241^0 C, IR spectrum (KBr,ν, cm^{-1}): 1610 (C=N), and 3246 (NH-pyrazole).^{1}H NMR (DMSO-d_6, δ ppm): 2.0 (s, 3H, CH_3), 5.8 (s, 1H, pyran), 7.5,8.2 (d, 4H, 4-NO_2 phenyl, Δ*J=11Hz*), 8.4 (s, 1H, triazole), 9.5 (s, 1H, pyrimidine) and 12.3 (s, 1H, NH pyrazole exchangeable with D_2O). MS, m/z (%): 349 (M^+, 23%), 227 [$(M\text{-}Ar)^+$, 100%].

8-Acetyl -8,11-dihydro-11(3-methoxyphenyl)-2,10-dimethylpyrazolo-[4`,3`:5,6]pyrano[2,3-e] [1,2,4]triazolo[1,5-c]pyrimidine 9c 52%,m.p 231-233^0 C IR spectrum (KBr,ν, cm^{-1}): 1721 (CO-CH_3). ^{1}H NMR (*CDCl$_3$,* δ ppm): 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 2.8 (s, 3H, $COCH_3$), 3.6 (s, 3H, OCH_3), MS, m/z (%): 390 (M^+, 5.5 (s, 1H, pyran), 6.6-7.3 (m, 4H, aromatic) and 9.0 (s, 1H, pyrimidine). 49%), 348 [(M-acetyl)$^+$, 11%] and 241 {[M-(Ac + Ar)]$^+$, 100%}.

8-Acetyl -8,11-dihydro-11(4-nitrophenyl)-2,10-dimethylpyrazolo-[4`,3`:5,6]pyrano[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine 9d: 60%,m.p 234-235^0 C IR spectrum (KBr,ν, cm^{-1}): 1750 (CO-CH_3) and absence NH. ^{1}H NMR (*DMSO-d_6,* δ ppm): 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.8 (s, 3H, CO-CH_3), 5.6 (s, 1H, pyran), 7.6,8.4 (d, 4H, p-O_2NPh, Δ*J=11Hz*) and 9.5 (s, 1H, pyrimidine). MS, m/z (%): 363 [(M-acetyl)$^+$, 22%], 241 {[M-(Ar+Ac)]$^+$, 100%}.

8,11-Dihydro-10-methyl-11-(4-nitrophenyl)pyrazolo-[4`,3`:5,6]-pyrano[2,3-e] [1,2,4]triazolo [1,5-c] pyrimidin-2-amine 10 : A mixture of compound 7b 0.3g (0.001 mol) and cyanogen bromide 0.1g (0.001 mol) in dimethylformamide (DMF) (10 ml), was refluxed for 5 h then left to cool. A solid was formed then collected by filteration and recrystallized from methanol to give 80% of compound 10. m.p. 293-295°C. ^{1}H NMR (*DMSO-d_6,* δ ppm): 2.0 (s, 3H, CH_3), 5.8 (s, 1H, pyran), 7.6 (d, 2H, aromatic, Δ*J=11Hz*), 8.1 (d, 2H, aromatic, Δ*J=11Hz*), 8.4 (s, 2H, NH_2), 9.7 (s, 1H, pyrimidine) and 12.4 (br, 1H, NH pyrazole).

2-Dichloromethyl-8,11-dihydro-10-methyl-11-(4-nitro-phenyl)pyrazolo[4`,3`:5,6]pyrano[2,3-e][1,2,4]triazolo-[1,5-c]pyrimidine 12a : A mixture of compound 7b **0**.3g (0.001 mol) and dichloroacetic acid 0.1g (0.001 mol) in phosphoryl chloride (10 ml), was heated under reflux for 8 h. The reaction mixture was poured onto crushed ice, then the obtained solid was collected by filteration and recrystallized from methanol to give 70% of compound **12**a. m.p. 250-253°C. ^{1}H NMR (*DMSO-d_6,* δ ppm): 2.1 (s, 3H, CH_3), 5.6 (s, 1H, pyran), 7.4 (s, 1H, NH exchangeable with D_2O), 7.5 (d, 2H, aromatic, Δ*J=11Hz*), 8.3 (d, 2H, aromatic, Δ*J=11Hz*), 9.5 (s, 1H, pyrimidine) and 12.3 (s, NH-pyrazole). MS, m/z (%): 435 (M^+, Cl^{37}, Cl^{37}, 1.44%), 433 (M^+, Cl^{37}, Cl^{35}, 8.17%), 431 (M^+, Cl^{35}, Cl^{35}, 13%) and 313 [(M, Cl^{37}, Cl^{37}-Ar)$^+$, 9.25%], 311 [(M, Cl^{37}, Cl^{35}-Ar)$^+$, 44.5%], 309 [(M, Cl^{35}, Cl^{35}-Ar)$^+$, 75%].

11-Aryl-8,11-dihydro-10-methyl-2-substituted-pyrazolo[4`,3`:5,6[-pyrano[2,3-e][1,2,4[triazolo-[1,5-c]pyrimidine 12 b,c, **13**a,b

General method: Equimolar amounts of compounds 7a 0.3g or 7b 0.3g (0.001 mol) and appropriate carboxylic acid (0.0015 mol) in phosphoryl chloride (10 ml) were heated under reflux for 10 h. The reaction mixture was poured onto crushed ice and the obtained solid, was collected by filteration and recrystallized from methanol to give compounds **12**b, **12**c, **13**a, **13**b , respectively

8,11-dihydro-10-methyl-11-(3-methoxyphenyl)-2-trichloromethyl-pyrazolo[4`,3`:5,6[-pyrano[2,3-e][1,2,4]triazolo-[1,5-c]pyrimidine 12b: 60%. m.p. 273-275°C. IR spectrum (KBr,ν, cm^{-1}): 1625 (C=N) and 3220 (NH). ^{1}H NMR (*DMSO-d_6,* δ ppm): 2.0 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 5.6 (s, 1H, pyran), 6.7-7.3 (m, 4H, aromatic), 9.6 (s, 1H, pyrimidine) and 12.3 (1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 456 (M^+, Cl^{37}, Cl^{37}, Cl^{37}, 1.4%), 454 (M^+, Cl^{37}, Cl^{37}, Cl^{35}, 10.5%), 452 (M^+, Cl^{37}, Cl^{35}, Cl^{35}, 30.8%), 450 (M^+, Cl^{35}, Cl^{35}, Cl^{35}, 33.7%) and 349 [(M, Cl^{37}, Cl^{37}, Cl^{37}-Ar)$^+$, 3.08%], 347 [(M, Cl^{37}, Cl^{37}, Cl^{35}-Ar)$^+$, 26.9%], 345 [(M, Cl^{37}, Cl^{35}, Cl^{35}-Ar)$^+$, 99.8%], 343 [(M, Cl^{35}, Cl^{35}, Cl^{35}-Ar)$^+$, 100%].

8,11-dihydro-10-methyl-11-(4-nitrophenyl)-2-trichloromethyl-pyrazolo[4`,3`:5,6[-pyrano[2,3-e][1,2,4]triazolo-[1,5-c]pyrimidine 12c: 62%. m.p. 167-169°C. ^{1}H NMR of compound **12**c (*DMSO-d_6,* δ ppm): 2.1 (s, 3H, CH_3), 5.7 (s, 1H, pyran), 7.6 (d, 2H, aromatic, AB system), 8.3 (d, 2H, aromatic, AB system) and 9.5 (s, 1H, pyrimidine). MS, m/z (%): 469 (M^+, Cl^{37}, Cl^{37}, Cl^{35}, 0.03%), 467 (M^+,

Cl^{37}, Cl^{35}, Cl^{35}, 4.34%), 465 (M^+, Cl^{35}, Cl^{35}, Cl^{35}, 5.66%) and 349 [(M^+, Cl^{37}, Cl^{37}, Cl^{37}-Ar)$^+$, 3.7%], 347 [(M, Cl^{37}, Cl^{37}, Cl^{35}-Ar)$^+$, 15%], 345 [(M, Cl^{37}, Cl^{35}, Cl^{35}-Ar)$^+$, 100%], 343 [(M, Cl^{35}, Cl^{35}, Cl^{35}-Ar)$^+$, 85%].

8,11-dihydro-10-methyl-2-phenyl)-11-(4-nitrophenyl)-pyrazolo[4`,3`:5,6]pyrano[2,3-e][1,2,4]triazolo[1,5-c]-pyrimidine 13a: 72%. m.p. 185-187°C. ^{1}H NMR (DMSO-d_6, δ ppm): 2.0 (s, 3H, CH_3), 5.6 (s, 1H, pyran), 7.4-8.3 (m, 14H, aromatic), 9.6 (s, 1H, pyrimidine) and 12.5 (s, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 425 (M^+, 16%), 303 [(M-Ar)$^+$, 100%] and 226 {[M-(Ar+Ph)]$^+$, 17%}.

8,11-dihydro-10-methyl-2,11-(4-nitrophenyl)-pyrazolo[4`,3`:5,6]pyrano[2,3-e][1,2,4]triazolo[1,5-c]-pyrimidine 13b : 62%. m.p. 200-201°C. IR spectrum (KBr,ν, cm^{-1}): 1622 (C=N) and 3195-3353 (NH pyrazole). The mass spectrum of **13b** , m/z (%): 470 (M^+, 20%), 348 [(M-Ar)$^+$, 33%].

4-Aryl-1,4-Dihydro-5-Imino-3-methyl-pyrazolo[4`,3`:5,6]-pyrano[2,3-d]pyrimidin-6-benzylidene amine 14a,b :A mixture of compound 7b 0.4g (0.001 mol), benzaldehyde, 0.1g (0.001 mol) and and p-nitro benzaldehyde, 0.15g (0.01 mol) in acetic acid (10 ml) was heated under reflux for 4 h. The solid formed on cooling, was collected by filteration and recrystallized from ethanol to give **14**a,**14**b respectively.

1,4-Dihydro-5-Imino-3-methyl-4-(4-nitrophenyl)-pyrazolo[4`,3`:5,6]-pyrano[2,3-d]pyrimidin-6-benzylidene amine 14a : 79%,M.p. 245-247°C. ^{1}H NMR of compound **14**a (DMSO-d_6, δ ppm): 2.1 (s, 3H, CH_3), 5.8 (s, 1H, pyran), 7.4 (s, 1H, N=CH), 7.5-8.1 (m, 9H, aromatic), 8.3 (s, 1H, pyrimidine), 10.9 (br, 1H, NH imino, exchangeable with D_2O) and 12.3 (br, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 427 (M^+, 7%), 323 [(M-N=CH-Ph)$^+$, 100%] and 202 {[M-(N=CHPh+Ar)]$^+$, 27%}.

1,4-Dihydro-5-imino-3-methyl-4-(4-nitrophenyl)- pyrazolo[4`,3`:5,6]pyrano]2,3-d]pyrimidin-6-(4-nitrobenzylidene) amine 14b recrystallized from petrolum ether (60-80) to give 70% of compound **14**b. m..p. 303-305°C. ^{1}H NMR (*DMSO-d_6*, δ ppm): 2.1 (s, 3H, CH_3), 6.0 (s, 1H, pyran), 7.4-8.3 (m, 9H, aromatic + N=CH), 8.4 (s, 1H, pyrimidine), 11.1 (s, 1H, NH imino, exchangeable with D_2O) and 12.3 (br, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 472 (M^+, 4%), 348 [(M-Ar)$^+$, 53%], 323 [(M-N=CHAr)$^+$, 100%], 202 {[M-(N=CHAr+Ar)]$^+$, 54%}.

1,4-Dihydro-3-methyl-4-(4-nitrophenyl)pyrazolo-[4`,3`:5,6]pyrano[2,3-d]pyrimidin-5-yl-4-nitrobenz-carbaldehyde bydrazone 15: A mixture of compound 7b, 0.3g (0.001 mol) and 4-nitro benzaldehyde, 0.15g (0.01 mol) in ethanol (10 ml) and two drops of piperidine. The reaction mixture was refluxed for 1 h and left to cool. A solid was obtained and collected by filteration and recrystallized from petrolum ether (60-80) to give 70% of compound **15**. m.p. 292-295°C. (*DMSO-d_6*, δ ppm): 2.1 (s, 3H, CH_3), 5.9 (s, 1H, pyran), 7.4-8.4 (m, 11H, aromatic + N=CH), 8.8 (s, 1H, NH), 9.7 (s, 1H, pyrimidine) and 12.4 (br, 1H, NH pyrazole, exchangeable with D_2O). MS, m/z (%): 472 (M^+, 5%), 348 [(M-Ar)$^+$, 100%].

Refrences

1-Diana, G. G.; Carabateas, P. M.; William, G. L.; Panicic, I.; Steinberg, B. A. *J. Med. Chem.* **1981**, 24, 431.

2-Elmoghayar, M. R. H.; Ibrahim, M. K. A.; Elsakka, I.; Elghandour, A. H. H. *Arch. Pharm.* **1983**, 316, 697.

3- Sugiura, S.; Ohno, S.; Wakayama, T. *J. Pharm. Soc. Jpn.* **1982**, 97, 791.

4- Kuo, S. C.; Huang, L. J.; Nakamura, H. *J. Med. Chem.* **1984**, 27, 539.

5- Chantegral, B.; Nadi, A.; Gelin, S. *J. Heterocycl. Chem.* **1985**, 22(1), 81.

6- Nawwar, G. A. M.; Abdel-Razak, F. M.; Swellam, R. H. *Arch. Pharm.* (Weinheim) **1991**, 324(11), 875.

7- Riad, B. Y.; Abdel Hamid, A. O.; Khalifa, F. A.; Youssry, Y. E. *Arch. Pharm. Res.***1989**, 12(3), 201

8- Esanu, A.; *Fr. Demande* FR 2,563,223 (Cl. Co 7H19/02), Oct 1985, GB Appl. 84/10,485, Apr 1984; *Chem. Abstr.* **1986**, 105, 172994e.

9- a, M.E.A.Zaki, , *Molecules*, **1998**, 3, 71. b, Nevine A. Abdallah, M.E.A.Zaki, *Acta Pharma.*, **1999** , 49, 159. c, S.A.Swelam, O.S. Abd El-Salam and M.E.A.Zaki, , *J.Serb. Chem. Soc.* **1999**, 64 (11), 655. d, M.E.A.Zaki, M.Fernanda Proenca, Brain L.Booth, *Journal of Organic Chemistry*, **2003**, *68(2);282.*

10- Arakawa, K.; Miasaka, T.; Ochi, H. *Chem. Pharm. Bull.* **1974**, 22(1),

11- Kuo, S. C.; Huang, L. J.; Nakamura, H. *J. Med. Chem.* **1984**, 27, 539.

12- Reddy, G. S.; Mandell, L.; Galdstein, J. H. *J. Chem. Soc.* **1963**, 1414.

13- Moneer, A. A.; Ismail, M. M.; Osman, A. N.; Fattah, B.; Abdel Ghoneim, K. M.; *Egypt. J. Pharm Sci.* **1993**, 34, 623.

14- Ismail, K. A.; Abulwafa, O. M.; Koreish, E. *Farmaco* **1995**, 50, 611.

15- Pathak, U.S.; Singh, S.; Padh, J. *Indian J. Chem. Sect.*B, **1991**, 30B, 618.

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